CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

50-779

MEDICAL REVIEW

AUG 16 2000

MEDICAL OFFICER REVIEW OF ORIGINAL NDA 50-779

Date of Submission: August 25, 1999
Date Review Completed: June 14, 2000

Applicant: B. Braun Medical Inc.
2525 McGaw Avenue
P.O. Box 19791
Irvine, CA. 92623

Regulatory Contact: John G. D'Angelo, M. S., R. Ph.

DRUG PRODUCT INFORMATION

Proprietary Name: Cefazolin for Injection and Dextrose Injection in the Duplex™ Container

Established Name: Cefazolin for Injection USP and Dextrose Injection USP

Dosage Form: Sterile lyophilized dry powder packaged with dextrose solution

Route of Administration: Intravenous (IV)

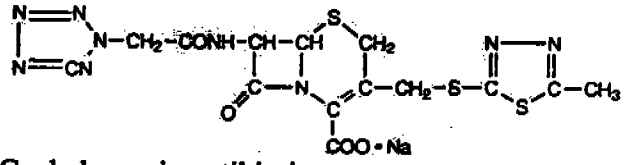
Cefazolin Sodium USP

Chemical Name: 3-{[(5-methyl-1, 3, 4-thiadiazol-2-yl)thio]-methyl}-8-oxo-7-[2-(1H-tetrazol-1-yl) acetamido]-5-thia-1-azabicyclo[4.2.0] oct-2-ene-2-carboxylic acid

Chem. formula: $C_{14}H_{13}N_8NaO_4S_3$

Molecular weight: 476.50

Chem. structure:



Drug Category: Cephalosporin antibiotic

Dosage Strength: 500 mg or 1 gram

Dextrose USP

Chemical Name: D-glucose monohydrate

Chemical Formula: $C_6H_{12}O_6 \cdot H_2O$

Molecular weight: 198.17

Dosage Strength: 2.4 g or 2.0 g (with 500 mg or 1 g of cefazolin, respectively)

RESUME

Cefazolin sodium is a cephalosporin antibiotic that has been marketed in the U. S. and worldwide. This antibiotic is packaged as a sterile, lyophilized dry powder with a dextrose solution. Cefazolin sodium and the dextrose solution are packaged in a two-chamber container system. This Duplex™ container is designed to deliver either a 500-mg or 1-gram dose of cefazolin [redacted] respectively. This New Drug Application (NDA), submitted under section 505 (b)(2) of the Federal Food, Drug, and Cosmetic Act, does not contain any clinical studies. The main body of this document consists of a review of the proposed product label.

BACKGROUND INFORMATION

Cefazolin sodium has been marketed in the U.S. for many years. The original patent for cefazolin (U.S. Patent No. 3,516,997) was issued to Fujisawa Pharmaceutical Co. on June 23, 1970. It expired on June 23, 1987. Cefazolin has been marketed in the 500-mg and 1-gram dose strengths as Ancef® by SmithKline Beecham Pharmaceuticals. The application for Ancef® (NDA 50-461) was approved prior to 1982 and is the reference listed drug. Cefazolin is currently marketed by several different manufacturers in the U.S. The cefazolin for injection used by B. Braun Medical Inc. contains the same active and inactive ingredients as the reference listed drug Ancef®. B. Braun Medical Inc. is seeking approval for the same indications as labeled for Ancef®.

On June 12, 1997, representatives from B. Braun Medical Inc. met with members of the Division of Anti-Infective Drug Products and other agency representatives to discuss the Duplex™ container system and the sponsor's plans to market cefazolin in the Duplex™ container. The discussions at that meeting led to the submission of this new drug application.

CHEMISTRY AND MANUFACTURING CONTROLS

Please see the CMC review by Andrew Yu, Review Chemist, for detailed descriptions of the drug product and manufacturing processes. The active pharmaceutical ingredient in this drug product is sterile cefazolin sodium. Cefazolin is supplied to the sponsor as a sterile lyophilized powder from _____ The drug substance supplier has given right of reference to the drug master file____ for this drug product. Cefazolin sodium is an official monograph of the United Sates Pharmacopeia.

The container system and final form of the drug product are produced by B. Braun Medical Inc. at its manufacturing facility in Irvine, CA. Stability testing is also performed at this manufacturing site. The Duplex™ container is a dual chamber drug delivery system that has been patented by the sponsor. The container has two chambers: one for the sterile, lyophilized cefazolin sodium powder (500 mg or 1 gram), and the other for the dextrose injection diluent (50 mL of 4.8% or 4.0% dextrose, respectively). There are two seals that must be peeled off for administration of the drug. The first seal separates the lyophilized powder from the diluent. After this seal is removed, pressure is applied to the diluent chamber to allow mixing of the powder and diluent. After mixing, pressure is applied to the drug solution to open the second seal. The second seal prevents clogging of the set port with the dry powder. The sponsor states that the product "is designed to prevent inadvertent administration of the drug or diluent alone".

(M. O. Comment: The product is designed to deliver either a 500-mg or 1-gram dose of cefazolin dissolved [redacted] respectively. Lyophilized cefazolin sodium dissolves readily in water, which should allow for complete dissolution of cefazolin in the diluent with little effort. This Duplex™ container system may not be appropriate for other drug substances that are less soluble. This will not affect the approval of this drug product. Dissolution of the drug substance should be considered in future applications that involve this container system.

Several deficiencies were noted in the CMC review dated April 11, 2000. Reportedly, the sponsor has addressed these deficiencies. At the time this document was written, the re-inspection of the Irvine, CA facilities was pending.)

PHARMACOLOGY/TOXICOLOGY INFORMATION

The pharmacology/toxicology review for this drug product was written by Ken Seethaler, Ph.D. The sponsor has not provided any new non-clinical pharmacology or toxicology studies for this drug product. The sponsor refers to the product information in the label for SmithKline Beecham's Ancef® brand of cefazolin sodium.

(M. O. Comment: The use of information from the Ancef® label is appropriate, given that the same USP monograph covers both the B. Braun drug substance and the SmithKline Beecham product.)

MICROBIOLOGY

Please see the microbiology review by Sousan Altaie, Ph.D., for details of the microbiology for this drug product. The sponsor has not provided any new microbiology studies. The sponsor refers to the product information in the label for the SmithKline Beecham product.

(M. O. Comment: The microbiology section of the SmithKline Beecham product has not been updated as requested in a letter to NDA holders in January, 1992. The pending microbiology review will address any changes needed to update the MICROBIOLOGY section of the product label for the B. Braun Medical Inc. drug product.)

CLINICAL PHARMACOKINETICS AND BIOPHARMACEUTICS

As with the microbiology and pharmacology/toxicology for this drug product, the sponsor has not provided any new clinical studies for this product. The basis for the CLINICAL PHARMACOLOGY section of the product label is the package insert for the SmithKline Beecham product. It should be noted that the Ancef® label contains information on the pharmacokinetics of cefazolin sodium following intravenous, intramuscular, and intraperitoneal administration. The B. Braun Medical Inc. product is designed for intravenous administration only. The sponsor has removed most references to intramuscular administration of cefazolin from the proposed label.

(M. O. Comment: The use of clinical pharmacology information from the Ancef® label is appropriate. However, pharmacokinetic information based on intramuscular or intraperitoneal administration of cefazolin should not be included in the B. Braun product label. The M.O.'s proposed changes are given in the clinical section of this review.)

CLINICAL DATA

As with the microbiology, pharmacology/toxicology, and biopharmaceutics sections of this application, no new clinical studies have been performed. The basis for the product label is the package insert for the SmithKline Beecham product.

(M. O. Comment: Again, the use of product information from the SmithKline Beecham label appears to be appropriate. The B. Braun Medical Inc. and SmithKline Beecham drug products are expected to be therapeutically equivalent. Since no clinical studies were performed for this drug product, there is no financial disclosure information to be reviewed.)

There are several differences in the drug product that must be considered for appropriate labeling of the B. Braun product. The duplex container system is designed as

a single-use product to deliver a 500-mg or 1-gram dose of cefazolin sodium in 50mL of dextrose in water. Therefore, the label for the B. Braun product should reflect the following:

(1) The product is designed for intravenous administration. It is not an appropriate formulation for intramuscular or intraperitoneal administration. The product label should not include pharmacokinetic information related to intramuscular or intraperitoneal administration of cefazolin, since this information is not relevant to the B. Braun product.

(2) The product contains dextrose. The product label should include appropriate warnings or precautions related to the administration of dextrose as part of the drug product.

(3) The product is designed for single use and not designed to deliver a dose of less than 500 mg or 1 gram. Pediatric labeling should reflect that this product is not designed to deliver less than the full adult dose. The product should not be used in pediatric patients who require less than the full 500-mg or 1-gram dose to prevent potential overdose.

(4) The label should include directions for use of the Duplex™ container.

(M. O. Comment: Most of these issues have been addressed by the sponsor, but the additional labeling changes are proposed by the medical officer in the labeling review that follows this section.)

Additional statements related to hepatitis, cholestatic jaundice, interstitial nephritis, and other renal disorders have been excerpted from the Apothecon® product label for cefazolin for injection. This product was approved under ANDA 62-831 on Dec. 9, 1988. The sponsor also provided a literature report[1] of hepatitis associated with the use of cefazolin and metronidazole. Both hepatic dysfunction including cholestasis, and renal dysfunction have been noted as adverse events caused by cephalosporin-class antibiotics. Data from the Adverse Event Reporting System (AERS) for cefazolin included 29 reports of nephritis not otherwise specified (N.O.S.), 8 reports of interstitial nephritis, 47 reports of acute renal failure, 26 reports of renal failure N.O.S., and 8 reports of renal tubular necrosis. The AERS database also includes 16 reports of cholestatic jaundice, 20 reports of jaundice N.O.S., 16 reports of hepatocellular damage, 9 reports of hepatic failure, and 11 reports of hepatitis N.O.S.

(M. O. Comment: The addition of these hepatic and renal adverse reactions is acceptable given the reports in the AERS database, their inclusion in the Apothecon label, and the inclusion of hepatic and renal adverse events in cephalosporin-class labeling.)

The sponsor has not included cephalosporin-class labeling in the proposed label. The Ancef label does not include such class labeling, though most cephalosporin labels include such statements.

(M. O. Comment: The medical officer recommends that cephalosporin-class labeling should be included in the label for this product. This class labeling will allow inclusion of adverse events known to occur with cephalosporins, though not reported in the original NDA or included in subsequent NDA supplements.)

---

[1] Beyounnes et al., "Cytolytic acute hepatitis associated with cefazolin and metronidazole." Gastroenterol. Clin. Biol. 19:740-741, 1995.

LABELING REVIEW

This section of the review will provide the medical officer's proposed changes to the sponsor's proposed label. The sponsor's proposed label is based on the label for Ancef®. Changes proposed by the medical officer will be shown with underlined text or with strikeouts. The medical officer will make parenthetical comments in bold font, discussing proposed changes by the M.O. or differences between the sponsor's proposed label and the Ancef® label. It should be noted that the sponsor has replaced the word Ancef® with either cefazolin or Cefazolin for Injection USP and Dextrose Injection USP. In some sections (e.g. **Microbiology**), the medical officer has not made substantial changes, but expects that reviewers from other disciplines will propose changes.

DESCRIPTION

Cefazolin for Injection USP and Dextrose Injection USP is a sterile, nonpyrogenic, single use, packaged combination of Cefazolin Sodium USP (lyophilized) and sterile iso-osmotic diluent in the DUPLEX sterile container. The DUPLEX Container is a flexible dual chamber container.

After reconstitution the approximate osmolality for Cefazolin for Injection USP and Dextrose Injection USP is 290 mOsmol/kg.

The diluent chamber contains Dextrose Injection USP, an iso-osmotic diluent using Hydrous Dextrose USP in Water for Injection USP. Dextrose Injection USP is sterile, nonpyrogenic, and contains no bacteriostatic or antimicrobial agents. Hydrous Dextrose USP has the following structural (molecular) formula:

(M. O. Comment: Molecular formula shown in label.)

The molecular weight of Hydrous Dextrose USP is 198.17

The drug chamber is filled with sterile lyophilized Cefazolin Sodium USP, a semi-synthetic cephalosporin and has the following IUPAC nomenclature: Sodium (6R,-7R)-3-[[(5-methyl-1,3,4-thiadiazol-2-yl)thio]meth 1-8-oxo-7-[2-(1H-tetrazol-1-yl)acetamido]-5-thia-1-azabicyclo-[4.2.0]oct-2-ene-2- arboxylate. Cefazolin Sodium USP has the following structural formula:

(M. O. Comment: Molecular formula shown in label.)

The sodium content is 48 mg/g of cefazolin sodium.

Cefazolin Sodium USP is supplied as a lyophilized form equivalent to either 500 mg or 1 g of cefazolin. Dextrose hydrous USP has been added to the diluent to adjust osmolality (approximately 2.4 g and 2 g to 500 mg and 1 g dosages, respectively).

(M. O. Comment: The additional statement on dextrose content is similar to a statement in the Claforan® label. Quantitative information on the dextrose content of the diluent should be included in this section.)

After [redacted] the foil strip, activating the seals, and thoroughly mixing, the reconstituted drug product is intended for single intravenous use.

The DUPLEX dual chamber container is made from a specially formulated material. The product (diluent and drug) contact layer is a mixture of thermoplastic rubber and a polypropylene ethylene copolymer that contains no plasticizers. The safety of the container system is supported by USP biological evaluation procedures.

(M. O. Comment: The CMC reviewer may propose further changes.)

CLINICAL PHARMACOLOGY

[redacted]

Studies have shown that following intravenous administration of cefazolin to normal volunteers, mean serum concentrations peaked at approximately 185 mcg/mL and were approximately 4 mcg/mL at 8 hours for a 1 gram dose. The serum half-life for cefazolin is approximately 1.8 hours following IV administration.

In a study (using normal volunteers) of constant intravenous infusion with dosages of 3.5 mg/kg for 1 hour (approximately 250 mg) and 1.5 mg/kg the next 2 hours (approximately 100 mg), cefazolin produced a steady serum [redacted] at the third hour of approximately 28 mcg/mL.

Studies in patients hospitalized with infections indicate that cefazolin produces mean peak serum levels approximately equivalent to those seen in normal volunteers.

Bile levels in patients without obstructive biliary disease can reach or exceed serum levels by up to five times; however, in patients with obstructive biliary disease, bile levels of cefazolin are considerably lower than serum levels (< 1.0 mcg/mL).

In synovial fluid, the cefazolin level becomes comparable to that reached in serum at about 4 hours after drug administration.

Studies of cord blood show prompt transfer of cefazolin across the placenta.

Cefazolin is present in very low concentrations in the milk of nursing mothers.

Cefazolin is excreted unchanged in the urine. In the first 6 hours approximately 60% of the drug is excreted in the urine and this increases to 70% to 80% within 24 hours.

[redacted]

Controlled studies on adult normal volunteers, receiving 1 gram 4 times a day for 10 days, monitoring CBC, AST (SGOT), ALT (SGPT), bilirubin, alkaline

phosphatase, BUN, creatinine and urinalysis, indicated no clinically significant changes attributed to cefazolin.
(M. O. Comment: The sponsor added the AST, ALT, and the parentheses to the above sentence from the Ancef® label. The Microbiology and Disk Susceptibility subsections of the proposed label are not shown here. They are likely to face extensive revisions by the microbiology reviewer in order to follow the format in the NDA holder's letter of January 1992.)

INDICATIONS AND USAGE
Cefazolin for Injection USP and Dextrose Injection USP is indicated in the treatment of the following serious infections due to susceptible organisms:

RESPIRATORY TRACT INFECTIONS due to *Streptococcus pneumoniae*, *Klebsiella* species, *Haemophilus influenzae*, *Staphylococcus aureus* (penicillin-sensitive and penicillin-resistant) and group A beta-hemolytic streptococci. Injectable benzathine penicillin is considered to be the drug of choice in treatment and prevention of streptococcal infections, including the prophylaxis of rheumatic fever.
Cefazolin is effective in the eradication of streptococci from the nasopharynx; however, data establishing the efficacy of cefazolin in the subsequent prevention of rheumatic fever are not available at present.

URINARY TRACT INFECTIONS due to *Escherichia coli*, *Proteus mirabilis*, *Klebsiella* species and some strains of enterobacter and enterococci.

SKIN AND SKIN STRUCTURE INFECTIONS due to *Staphylococcus aureus* (penicillin-sensitive and penicillin-resistant), group A beta-hemolytic streptococci and other strains of streptococci.

BILIARY TRACT INFECTIONS due to *Escherichia c[illegible]* various strains of streptococci, *Proteus mirabilis*, *Klebsiella* species and [illegible]*aphylococcus aureus*.

BONE AND JOINT INFECTIONS due to *Staphylococcus aureus*.

GENITAL INFECTIONS (i.e., prostatitis, epididymitis) due to *Escherichia coli*, *Proteus mirabilis*, *Klebsiella* species and some strains of enterococci.

SEPTICEMIA due to *Streptococcus pneumoniae*, *Staphylococcus aureus* (penicillin-sensitive and penicillin-resistant), *Proteus mirabilis*, *Escherichia coli* and *Klebsiella* species.

ENDOCARDITIS due to *Staphylococcus aureus* (penicillin-sensitive and penicillin-resistant) and group A beta-hemolytic streptococci.

Appropriate culture and susceptibility studies should be performed to determine susceptibility of the causative organism to cefazolin.

PERIOPERATIVE PROPHYLAXIS: The prophylactic administration of cCefazolin preoperatively, intraoperatively and postoperatively may reduce the incidence of certain postoperative infections in patients undergoing surgical procedures which are classified as contaminated or potentially contaminated (e.g., vaginal hysterectomy, and cholecystectomy in high-risk patients such as those over 70 years of age, with acute cholecystitis, obstructive jaundice or common duct bile stones).

The perioperative use of cCefazolin may also be effective in surgical patients in whom infection at the operative site would present a serious risk (e.g., during open-heart surgery and prosthetic arthroplasty).

The prophylactic administration of cCefazolin should usually be discontinued within a 24-hour period after the surgical procedure. In surgery where the occurrence of infection may be particularly devastating (e.g., open-heart surgery and prosthetic arthroplasty), the prophylactic administration of cCefazolin may be continued for 3 to 5 days following the completion of surgery.

If there are signs of infection, specimens for cultures should be obtained for the identification of the causative organism so that appropriate therapy may be instituted.

(See DOSAGE AND ADMINISTRATION.)

(M. O. Comment: The INDICATIONS AND USAGE section above is based on the Ancef® label. Since the drug product by B. Braun Medical Inc. is expected to be therapeutically equivalent to the innovator product, Ancef®, it is appropriate for the INDICATIONS AND USAGE section to be substantially the same. The word "Ancef" was replaced with either cefazolin or Cefazolin for Injection USP and Dextrose Injection USP throughout the label. Since the indications shown are from the Ancef® label, they are not specific to Cefazolin for Injection USP and Dextrose Injection USP. The medical officer recommends that the term cefazolin be used in this section, except for the first sentence, which is meant to be specific for the drug product being labeled.)

CONTRAINDICATIONS

CEFAZOLIN FOR INJECTION USP AND DEXTROSE INJECTION USP IS CONTRAINDICATED IN PATIENTS WITH KNOWN ALLERGY TO THE CEPHALOSPORIN GROUP OF ANTIBIOTICS.

Solutions containing dextrose may be contraindicated in patients with hypersensitivity to corn products.

(M. O. Comment: The sponsor added the sentence regarding corn products. Support for the inclusion of this statement has not been provided. The statement is included in the product label for 5% Dextrose Injection USP produced by B. Braun Medical Inc. The medical literature includes reports of patients with allergic reactions to solutions containing dextrose or other carbohydrates derived from corn products. Recommendations against use of this product in patients with

hypersensitivity to corn products seem prudent, given that other formulations of cefazolin are generally available for use. The statement is acceptable.
The WARNINGS section is not shown here. The sponsor has not modified the label for the SmithKline product, except for the name change from "Ancef".)

PRECAUTIONS

General

Prolonged use of Cefazolin for Injection USP and Dextrose Injection USP may result in the overgrowth of nonsusceptible organisms. Careful clinical observation of the patient is essential.

When Cefazolin for Injection USP and Dextrose Injection USP is administered to patients with low urinary output because of impaired renal function, lower daily dosage is required (see DOSAGE AND ADMINISTRATION).

As with other beta-lactam antibiotics, seizures may occur if inappropriately high doses are administered to patients with impaired renal function (see DOSAGE AND ADMINISTRATION).

Cefazolin for Injection USP and Dextrose Injection USP, as with all cephalosporins, should be prescribed with caution in individuals with a history of gastrointestinal disease, particularly colitis.

As with other dextrose-containing solutions, Cefazolin for Injection USP and Dextrose Injection USP should be [redacted] with caution in patients with overt or known subclinical diabetes mellitus or carbohydrate intolerance for any reason.

If administration is controlled by a pumping device, care must be taken to discontinue pumping action before the container runs dry or air embolism may result.

Use only if solution is clear and container and seals are intact.

(M. O. Comment: The underlined statements are proposed additions by the medical officer. They are statements that appear in the 5% Dextrose USP product label made by B. Braun Medical Inc. Fluids containing dextrose are usually avoided in diabetic patients, in favor of saline solutions, to avoid hyperglycemia. Given that other formulations of this drug can be delivered without dextrose, it seems prudent to include a precaution related to the use of this drug product in diabetic patients. Other precautions from the 5% Dextrose USP label have not been included, because they do not apply to the intended use or design of the Cefazolin for Injection USP and Dextrose Injection USP product.)

Drug Interactions

Probenecid may decrease renal tubular secretion of cephalosporins when used concurrently, resulting in increased and more prolonged cephalosporin blood [redacted]

Drug/Laboratory Test Interactions

A false positive reaction for glucose in the urine may occur with Benedict's solution, Fehling's solution or with Clinitest® tablets, but not with enzyme-based tests such as Clinistix® and Tes-Tape®.

Positive direct and indirect antiglobulin (Coombs) tests have occurred; these may also occur in neonates whose mothers received cephalosporins before delivery.

Carcinogenesis/Mutagenesis

Mutagenicity studies and long-term studies in animals to determine the carcinogenic potential of Cefazolin for Injection USP and Dextrose Injection USP have not been performed.

Pregnancy Teratogenic Effects Pregnancy Category B.

Reproduction studies in rats, There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Labor and Delivery

When cefazolin has been administered prior to caesarean section, drug levels in cord blood have been approximately one quarter to one third of maternal drug The drug appears to have no adverse effect on the fetus.

Nursing Mothers

Cefazolin is present in very low concentrations in the milk of nursing mothers. Caution should be exercised when Cefazolin for Injection USP and Dextrose Injection USP is administered to a nursing woman.

Pediatric Use

Cefazolin for Injection USP and Dextrose Injection USP is designed to deliver a 500 mg or 1 g dose of cefazolin. To prevent unintentional overdose, Cefazolin for Injection USP and Dextrose Injection USP should not be used in pediatric patients who require less than the full adult dose of cefazolin.

The potential for the toxic effect in children from chemicals that may leach from the single-dose IV preparation in plastic has not been determined.

(M. O. Comment: The sentence added by the medical officer is intended to promote the safe use of this product in pediatric patients. The drug product is designed as a single use product to deliver a full 500-mg or 1-g dose of cefazolin. The sponsor has included instructions in the DOSAGE AND ADMINISTRATION section of the label to deliver part of a full dose by using an infusion pump or a buret. These instructions pose a risk to patients of unintentional overdose of cefazolin. Other formulations of cefazolin, which can be prepared by pediatric pharmacists and administered as a unit dose, are available and do not pose this same risk. Given these facts, the medical officer recommends the Pediatric Use statement be modified as shown. The medical officer has deleted the statement about "prematures and infants" since it would not be applicable with the stated dosage precaution. The

statement about chemicals that may leach from the IV preparation in plastic was carried over by the sponsor from the Ancef® label. It has not been changed by the medical officer, pending further recommendations by the CMC reviewer.)

ADVERSE REACTIONS

The following reactions have been reported:

Gastrointestinal: Diarrhea, oral candidiasis (oral thrush), vomiting, nausea, stomach cramps, anorexia and pseudomembranous colitis. Onset of pseudomembranous colitis symptoms may occur during or after antibiotic treatment (see WARNINGS). Nausea and vomiting have been reported rarely.

Allergic: Anaphylaxis, eosinophilia, itching, drug fever, skin rash, Stevens-Johnson syndrome.

Hematologic: Neutropenia, leukopenia, thrombocytopenia, thrombocythemia.

Hepatic and Renal: Transient rise in AST (SGOT), ALT (SGPT), BUN and alkaline phosphatase [redacted] has been observed without clinical evidence of renal or hepatic impairment. Interstitial nephritis and other renal disorders have been reported rarely. Most patients experiencing these reactions have been seriously ill and were receiving multiple drug therapies. The role of cefazolin in the development of nephropathies has not been determined. As with some penicillins and some other cephalosporins, transient hepatitis and cholestatic jaundice have been reported rarely.

(M. O. Comment: Only the first sentence in the Hepatic and Renal subsection is part of the Ancef® label. The remainder of this section is excerpted from the label for cefazolin produced by Apothecon®, a Bristol-Myers Squibb company. Hepatitis, cholestatic jaundice, interstitial nephritis and other renal disorders are added to the adverse reactions for cefazolin. The addition of these conditions is acceptable to the medical officer.)

Local Reactions: Rare instances of phlebitis have been reported at site of injection. Some induration has occurred.

Other Reactions: Genital and anal pruritus (including vulvar pruritus, genital moniliasis and vaginitis).

Cephalosporin-class Adverse Reactions: In addition to the adverse reactions listed above that have been observed in patients treated with cefazolin, the following adverse reactions and altered laboratory tests have been reported for cephalosporin-class antibiotics:

Adverse Reactions: Allergic reactions, urticaria, serum sickness-like reaction, erythema multiforme, toxic epidermal necrolysis, colitis, renal dysfunction, toxic nephropathy, abdominal pain, reversible hyperactivity, hypertonia, hepatic dysfunction including cholestasis, aplastic anemia, hemolytic anemia, hemorrhage, and superinfection.

Altered Laboratory Tests: Prolonged prothrombin time, positive direct Coombs' test, false-positive test for urinary glucose, elevated bilirubin, elevated LDH, increased creatinine, pancytopenia, and agranulocytosis.

Several cephalosporins have been implicated in triggering seizures, particularly in patients with renal impairment when the dosage was not reduced (see **DOSAGE AND ADMINISTRATION**). If seizures associated with drug therapy

occur, the drug should be discontinued. Anticonvulsant therapy can be given if clinically indicated.

(M. O. Comment: This added section describes cephalosporin-class adverse reactions, and is similar to class labeling for other cephalosporins. The Ancef® label does not include similar class labeling. Adverse events that are usually included in the class labeling, but are included elsewhere in the ADVERSE EVENTS section, were removed from the class labeling statement.)

DOSAGE AND ADMINISTRATION

Usual Adult Dosage

Type of Infection	Dose	Frequency
Moderate to severe infections	500 mg to 1 gram	every 6 to 8 hours
Mild infections caused by susceptible gram + cocci	500 mg	every 8 hours
Acute, uncomplicated urinary tract infections	1 gram	every 12 hours
Pneumococcal Pneumonia	500 mg	every 12 hours
Severe, life-threatening infections (e.g., endocarditis, septicemia)*	1 gram to 1.5 grams	ry 6 hours

*In rare instances, doses of up to 12 grams of cefazolin per day have been used.

(M. O. Comment: Since the product is not designed to deliver a dose of less than 500 mg, the usual adult dosages in the DOSAGE AND ADMINISTRATION section for this product should only refer to multiples of 500 mg.)

Perioperative Prophylactic Use

To prevent postoperative infection in contaminated or pctentially contaminated surgery, recommended doses are:

a. 1 gram IV administered 1/2 hour to 1 hour prior to the start of surgery.
b. For lengthy operative procedures (e.g., 2 hours or more), 500 mg to 1 gram IV during surgery (administration modified depending on the duration of the operative procedure).
c. 500 mg to 1 gram IV every 6 to 8 hours for 24 hours postoperatively.

It is important that (1) the preoperative dose be given just (1/2 to 1 hour) prior to the start of surgery so that adequate antibiotic [redacted] are present in the serum and tissues at the time of initial surgical incision; and (2) cCefazolin [redacted]

be administered, if necessary, at appropriate intervals during surgery to provide sufficient [redacted] of the antibiotic at the anticipated moments of greatest exposure to infective organisms.

In surgery where the occurrence of infection may be particularly devastating (e.g., open-heart surgery and prosthetic arthroplasty), the prophylactic administration of cCefazolin ~~for~~ [redacted] may be continued for 3 to 5 days following the completion of surgery.

Dosage Adjustment for Patients with Reduced Renal Function

Cefazolin [redacted] may be used in patients with reduced renal function with the following dosage adjustments: Patients with a creatinine clearance of 55 mL/min. or greater or a serum creatinine of 1.5 mg % or less can be given full doses. Patients with creatinine clearance rates of 35 to 54 mL/min. or serum creatinine of 1.6 to 3.0 mg % can also be given full doses but dosage should be restricted to at least 8 hour intervals. Patients with creatinine clearance rates of 11 to 34 mL/min. or serum creatinine of 3.1 to 4.5 mg % should be given 1/2 the usual dose every 12 hours. Patients with creatinine clearance rates of 10 mL/min. or less or serum creatinine of 4.6 mg % or greater should be given 1/2 the usual dose every 18 to 24 hours. All reduced dosage recommendations apply after an initial loading dose appropriate to the severity of the infection.

[redacted]

1 page(s) have been removed because it contains trade secret and/or confidential information that is not disclosable.

MEDICAL OFFICER CONCLUSIONS

The medical officer recommends approval of this NDA if there is concurrence from the other reviewing disciplines. The M. O. recommendations for changes to the product label should be conveyed to the sponsor.

/S/

John Alexander, M. D.

cc:
Original NDA #50-779
HFD-520
HFD-520/MO/Alexa[illegible]
HFD-520/TL/Soreth /S/ 9/16/00
HFD-520/PM/Duvall-Miller
HFD-520/DEPDIR/Gavrilovich
KEYWORDS:
ADMIN REVIEW
CLASS BETA-LACTAM CEPH
POP ADULT

Concurrence Only:
HFD-520/DIVDIR/CL[illegible]

/S/ 9/23/2000